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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,626	GAMBLE ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *21-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 and 25-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 April 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-43 are pending.

Election/Restrictions

Applicant's election with traverse of Group X, in the reply filed on 4/19/07 is acknowledged. The traversal is on the ground(s) that Groups I and X are related in that they would achieve the same effect. Applicants argue that although there are many differences in the means by which the nucleic acid is administered in vitro versus in vivo delivery, there is otherwise very little difference in terms of the outcome that one would expect using a nucleic acid molecule in vivo; in particular the functional level of sphingosine kinase in the endothelial cell is modulated irrespective of whether the nucleic acid is administered in vitro or in vivo. Applicants argue accordingly, it is considered that there is a clear technical relationship involving an expected effect shared by all the claims of both group I and group X in the modulation of the functional level of sphingosine kinase by use of a nucleic acid encoding sphingosine kinase. This argument is not persuasive because there are important differences in terms of the outcome of the effects on a cell when a nucleic acid encoding for sphingosine kinase is delivering in vitro vs in vivo. For example, a cell in vitro is exposed to different extracellular signals compared to a cell in vivo or in situ. Serum alone or serum free culture conditions have different effects on the expression of the SK in vitro compared to the same type of cell in vivo, where there are growth factors that are not present in vitro. As such there is no technical relationship among the conditions for expressing KS in vitro vs in vivo.

The requirement is still deemed proper and is therefore made FINAL.

Claims 21-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 4/19/07.

Claims 1-20 and 25-43 are under consideration.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

See page 46 and 54 for embedded hyperlinks.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 20 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim is drawn to a nucleic acid molecule encoding a sphingosine kinase functional equivalent, derivative of homologue thereof or the sphingosine kinase expression product or functional derivative, homologue, analogue, equivalent or mimetic thereof. The claim does not require that the produced protein possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claim is drawn to a

genus of nucleic acids that is defined only by sequence identity.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product or any combination thereof. In this case, there is no identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more that a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification discusses a " "variant"

of sphingosine kinase should be understood to mean molecules which exhibit at least some of the functional activity of the form of sphingosine kinase of which it is a variant. A variation may take any form and may be naturally or non-naturally occurring. A mutant molecule is one which exhibits modified functional activity". The genes coding for a sphingosine kinase functional equivalent, derivative of homologue thereof or the sphingosine kinase expression product or functional derivative, homologue, analogue, equivalent or mimetic thereof encompassed within the genus of genes coding for a sphingosine kinase protein, functional equivalents derivatives, homologues, analogs mimetics thereof, have not been disclosed. There is no evidence on the record where the specification teaches any characteristics of a sphingosine kinase functional equivalent, derivative of homologue thereof or the sphingosine kinase expression product or functional derivative, homologue, analogue, equivalent or mimetic that would distinguish it from a non-natural variant constructed by the hand of man.

In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by a member of the genus of SK capable of modulating endothelial cell functional characteristics in vivo. Therefore, Applicant was not in possession of the genus of saliva specific *cis*-acting elements as encompassed by the claims. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." The specification provides evidence of possession for overexpression of sphingosine kinase by introducing an adenovirus containing sphingosine kinase enhances cell survival of human umbilical vein endothelial cells (HUVEC) in vitro (example 1). The specification also provides evidence for overexpression of sphingosine kinase alters adhesion molecule expression in HUVEC,

enhances neutrophil adhesion to endothelial cells and promotes tube formation or the endothelial cells arrange into a capillary like network (tubes) in vitro, (example 2).

Claims 1-20 and 25-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method for modulating one or more mammalian endothelial cell functional characteristics by modulating the functional level of sphingosine kinase (SK) wherein inducing overexpression of the sphingosine kinase level modulates the functional characteristics of said endothelial cells. Claims are also directed to a method for treatment and/or prophylaxis of a condition characterized by aberrant or otherwise unwanted endothelial cell functioning in a mammal by modulating the functional level of sphingosine kinase in said mammal, wherein inducing overexpression of said sphingosine kinase level modulates functional characteristics of said endothelial cells.

The specification teaches that overexpression of sphingosine kinase by introducing an adenovirus containing sphingosine kinase enhances cell survival of human umbilical vein endothelial cells (HUVEC) in vitro (example 1). The specification also teaches that overexpression of sphingosine kinase alters adhesion molecule expression in HUVEC, enhances neutrophil adhesion to endothelial cells and promotes tube formation or the endothelial cells arrange into a capillary like network (tubes) in vitro, (example 2). The specification speculates that said tube formation in vitro correlates to angiogenesis and angiogenesis is a characteristic feature of many chronic inflammatory diseases (specification p 61). While the specification provides teachings pertaining to the effects of overexpression of SK

in cells in vitro, the specification fails to provide any relevant teachings or specific guidance or working examples with regard to the production of SK in vivo, by modulating the functional level of SK in a mammal resulting in the treatment and/or prophylaxis of a condition characterized by aberrant or otherwise unwanted endothelial cell function. The guidance provided by the instant specification fails to correlate the production of a therapeutic protein in vitro to production of a therapeutic protein in vivo resulting in treatment or prevention of disease. Thus, as enablement requires the specification to teach how to make and use the claimed invention, the specification fails to enable the claimed methods for treating and/or prophylaxis of a disease. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

At the time of filing the art taught that gene therapy was unpredictable without undue experimentation. With regard to gene therapy, while progress has been made in recent years for gene transfer in vivo, vector targeting to desired tissues in vivo continuous to be a difficulty as supported by teaching in the art. **Gnewuch et al,** (Cell Mol Life Sci, 59: 959-1023, 2002) while reviewing the status of gene therapy notes there have been several drawbacks to gene therapy including the inaccurate delivery of the gene to the desired cellular localization, the inaccurate transposition of the gene to the required place on the human genome and the lack of activity against metastasized cancer cells (p 992, 1st bridge 2nd column). **Gnewuch et al,** assessed gene therapy at that time is not developed to a point of predictable results in all patients (p 992, 2nd column, 2nd paragraph). **Cuvillier** (Anticancer Drugs, 18(2): 105010, 2007) even four years after the filing of the instant application notes sphingosine kinase controls the levels of sphingolipids having opposite effects on cell survival/death, its gene was found to be of oncogenic nature, its mRNA is overexpressed in many solid tumors, its overexpression protects cells from apoptosis and its activity is decreased during anticancer treatments (abstract).

Therefore, SK appears to be a potential therapeutic target in cancer (Cuvillier, abstract). While progress has been made in recent years for in vivo gene transfer, vector targeting in vivo to be desired organs continued to be unpredictable and inefficient. For example, numerous factors complicate the gene delivery art that could not have been overcome by routine experimentation. These include, the fate of DNA vector itself, volume of distribution, rate of clearance in tissue, the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of RNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced (Ecke et al , Goodman & Gilman's The Pharmacological basis of Therapeutics, McGraw-Hill, New York, NY. pp 77-101). Cell cultures, which is a n in vitro system is not directly correlatable to the treatment of a mammal which would be in vivo or in situ. The delivery of a vector to target tissue culture cells does not provide guidance cited above for overcoming the obstacles on in vivo delivery because the vector does not have to pass through the complex organization of organs and tissues. Cells cultures do no mimic organs in that there is no three-dimensional structure, blood vessels, connective tissue through which the vector would need to pass in vivo. Any data obtained from cells grown in vitro cannot be extrapolated to the in vivo situation. The instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of SK gene transfer in vivo resulting in the modulation of endothelia cell in vivo or in the treatment and/or prophylaxis of a disease raised by the state of the art.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the treatment of a disease by modulating the functional levels of SK in cells in vivo, the lack of direction or guidance provided by the specification for the treatment of

a disease by modulating the functional levels of SK in cells in vivo, the absence of working examples that correlate to the treatment of a disease, the unpredictable state of the art with respect to SK gene therapy, and for the treatment of a disease by modulating the functional levels of SK in cells in vivo, the undeveloped state of the art pertaining to the treatment and/or prophylaxis of a condition by SK gene therapy, and the breadth of the claims directed to all diseases and cell types, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 5, are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 15-20 of U.S. Patent No. 10275,686. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a method for modulating sphingosine kinase levels in a mammal or cell in vivo with a nucleic acid encoding for sphingosine kinase. The '689 claim 12

the malignant cell has become transformed by sphingosine kinase overexpression oncogenic activity.

Claims 1-2, 5-7, 15 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15, 17, 23, of U.S. Patent No. 09/977,217. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a method for modulating sphingosine kinase levels in a mammal or cell in vivo with a nucleic acid encoding for sphingosine kinase.

Claims 1-2, 5-7, 15, are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 32-38 of U.S. Patent No. 10/830677. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a method for modulating sphingosine kinase levels in a mammal or cell in vivo with a nucleic acid encoding for sphingosine kinase.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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